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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,200	11/08/2006	Rudolf Moser	EPROV-0024	4126

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EXAMINER	
STONE, CHRISTOPHER R	

ART UNIT	PAPER NUMBER
1614	

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12/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,200	MOSER ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER R. STONE	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed August 27, 2008, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments with respect to claims 1-17 and 19-24 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 19 is drawn to the composition of claim 1, which has a pH of greater than 8.5 to 9.5. There is no support, as filed, for this pH range.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is drawn to the composition of claim 1, "which has a pH of greater than 8.5 to 9.5." It is unclear whether the claim intends to encompass only values greater than 9.5 or values greater than 8.5, which may be less than 9.5.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-16 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Odin et al in view of Beggs et al (US 5,434,087) and Nijkerk et al (WO 95/26963). (All documents listed on PTO 1449, filed November 8, 2006)

Claims 1, 2, 4-16 and 19-24 are drawn to a pharmaceutical composition comprising 5,10-methylenetetrahydrofolic acid and citrate at a pH of 7.5 to 10.5.

Odin et al teaches a composition comprising the calcium salt of 5,10-(6R,S)-methylenetetrahydrofolic acid (CH_2FH_4) and optionally vitamin C (ascorbic acid, a reducing agent) at a pH of 8.95, prepared with and without the exclusion of atmospheric oxygen (p. 448, 2nd column, 3rd paragraph and p. 451, 1st column, 4th paragraph) useful in the biomodulation of 5-fluorouracil (5-FU) in the treatment of cancer (p. 454, 2nd column, 2nd paragraph). Odin does not teach the composition further comprising citrate. Beggs et al (US 5,434,087) teaches that citrate improves the stability of the reduced folic acid derivative 5-methyl-tetrahydrofolic acid (column 8, lines 31-35). Nijkerk et al (WO 95/26963) teaches that citrate is used as a stabilizer in pharmaceutical compositions and improves the stability of the reduced folic acid derivative, folinic acid (p. 1, line 37 to p. 2 line 4). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add citrate to the composition of Odin et al and to prepare the composition (or stabilize the composition of CH_2FH_4) by bringing the components together (i.e. treating the CH_2FH_4 with citrate) and adjusting the pH to 8.95, since citrate was known to improve the stability of reduced folate derivatives, thus resulting in the practice of the instantly claimed invention with a

reasonable expectation of success. As for claim 19, Odin further teaches that the stability of CH_2FH_4 is improved in more alkaline solutions (p. 453, right column, 2nd full paragraph), providing the motivation for one of ordinary skill in the art to increase the pH to greater than 8.5, thus resulting in the instantly claimed composition with a reasonable expectation of success. Odin further teaches that tetrahydrofolic acid (FH_4) is useful for the biomodulation of 5-fluorouracil (5-FU) in the treatment of cancer (p. 454, 2nd column, 2nd paragraph). Therefore it would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add FH_4 and/or 5-FU to the composition mentioned above, since FH_4 and the composition were known to be used for the same purpose and 5-FU and the composition where known to be useful when administered together. Applicant is reminded of in re Kerkhoven, which affirmed that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) Additionally, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to formulate the composition into a lyophilization solution and a lyophilate, since lyophilization is commonly used in the art to preserve pharmaceuticals.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Odin et al, Beggs et al (US 5,434,087) and Nijkerk et al (WO 95/26963) as applied to claims 1, 2, 4-16 and 19-24 above, further in view of Cobb et al (US Patent 5989566).

Claim 3 is drawn to a pharmaceutical composition comprising 5,10-methylenetetrahydrofolic acid, citrate and formaldehyde at a pH of 7.5 to 10.5.

Odin et al, Beggs et al and Nijkerk et al as combined supra teach the aforementioned composition, but do not teach the composition further comprising formaldehyde.

Cobb et al teaches that formaldehyde is used as a preservative in pharmaceutical formulations (column 6, lines 1-3). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add formaldehyde to the composition of 5,10-methylenetetrahydrofolic acid and citrate to preserve the components of the composition, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

In response to applicant's argument that the formaldehyde in the instantly claimed composition provides additional benefits other than the preservative activity taught by Cobb et al, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Odin et al in view of Beggs et al (US 5,434,087) and Nijkerk et al (WO 95/26963) as applied to claims 1, 2, 4-16 and 19-24 above, further in view of Rabelink et al (US PGPUB 2002/0052374) and Binderup (US PGPUB 2002/0183277).

Claim 17 is drawn to a pharmaceutical composition comprising 5,10-methylenetetrahydrofolic acid, citrate and capecitabine at a pH of 7.5 to 10.5.

Odin et al, Beggs et al and Nijkerk et al as combined supra teach the aforementioned composition, but do not teach the composition further comprising capecitabine.

Rabelink teaches that tetrahydrofolates are useful for increasing the therapeutic effects of fluorinated pyrimidines (paragraph [0002]). Binderup teaches that capecitabine is a fluorinated pyrimidine (paragraph [0032]).

Therefore it would have been prima facie obvious at the time the invention was made to add capecitabine to the composition of Odin et al, Beggs et al and Nijkerk, to potentiate the therapeutic effect of the drug, thus resulting in the practice of the instantly claimed invention with a reasonable expectation off success.

Claim Objections

Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The pH range of claim 19, encompasses pH values outside the pH range of claim 1, from which claim 19 depends.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER R. STONE whose telephone number is (571)270-3494. The examiner can normally be reached on Monday-Thursday, 7:30am-4:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Patricia A. Duffy/
Primary Examiner, Art Unit 1645